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Simultaneous quantification of Gabapentin, Sulfamethoxazole, Terbutryn, Terbutylazine and Diuron by UV-Vis spectrophotometer

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ABSTRACT

In this study, viable and accessible analytical method for the quantification of pharmaceuticals (Gabapentin, Sulfamethoxazole), herbicides and algicides (Terbutryn, Terbutylazine, Diuron) in the aquatic environment was developed. The studied compounds are priority pollutants listed by the Directives of the European Parliament and of the Council Amending Directives (2000/60/EC and 2008/105/EC). Estimation of gabapentin concentration through UV-Vis spectrophotometer shows high linearity and meets the validation criteria set by the International Council for Harmonisation (ICH). Sulfamethoxazole and pesticides determination method was set up using solid phase extraction and examined with UV-Vis spectrophotometer. A novel approach was developed through this study for the estimation of gabapentin concentration; which does not really require any solid phase extraction procedures. Gabapentin concentration can be directly analyzed with high accuracy using UV-Vis spectrophotometer in conjugation with ninhydrin reagent. Similarly, this research demonstrated the instantaneous detection of sulfamethoxazole by evaluating the factor obtained from the linear calibration curve method. On the other hand, pesticides/biocides are moderately hydrophilic thus require extraction technique. The successful extraction method is developed showing high recovery of desired compounds. The developed methods were incorporated with UV-Vis spectroscopy method, reliable and useful for routine laboratory analysis.

Keywords: Spectrophotometry, extraction, pharmaceuticals, triazines, phenyl urea.

1. INTRODUCTION

Gabapentin and sulfamethoxazole are two widely used pharmaceuticals; prominently dispersed, detected in an aquatic environment including ground, surface water, and domestic and municipal wastewater [1]–[4]. Gabapentin (1-(aminomethyl) cyclohexane acetic acid) is commonly used as the antiepileptic drug in clinical practice. It is the active ingredients of Neurontin: used for preventing and controlling seizures.

Sulfamethoxazole(4-Amino-N-(5-methyl-3-isoxazolyl) benzenesulfonamide), falls in sulphonamide class which are generally deployed for its bacteriostatic activity commonly urinary infection treatment [3, 5]. According to Intercontinental Marketing Services (IMS) Health report, gabapentin and sulfamethoxazole are majorly used in clinical practice and possess severe adverse effect to a human if overdosed [6,7].

The pesticides industries manufacture synthetic chemicals to provide protection to an agricultural field. Triazines: Terbutryn, Terbutylazine and phenyl urea Diuron are wide range algicides and herbicides, used to prevent and control the growth of weeds, grasses, mosses and algae in agricultural crops with protruding effects by inhibiting photosynthesis. These can also be directly added to water to prevent the growth of aquatic herbicides [8]. In spite of economic benefit, the prolonged exposure results in contaminating the environment. Also, continued occurrence in environment cause toxicity to plants other than weeds. By extensive time use, due to discharge from domestic, industrial and agricultural pits, it can reach sewerage waters by drainage[9]. Diuron possesses leaching property and may also leach into groundwater causing groundwater pollution [10].

The proposals of Directives of the European Parliament and of the Council amending Directives 2000/60/EC and

2008/105/EC list these compounds as priority substance in the field of water policy stated in Annex X to the Water Framework Directives (WFD) 2000/60/EC. It states the significant risk of compounds to or via aquatic environment. The structures are shown in Figure 1.

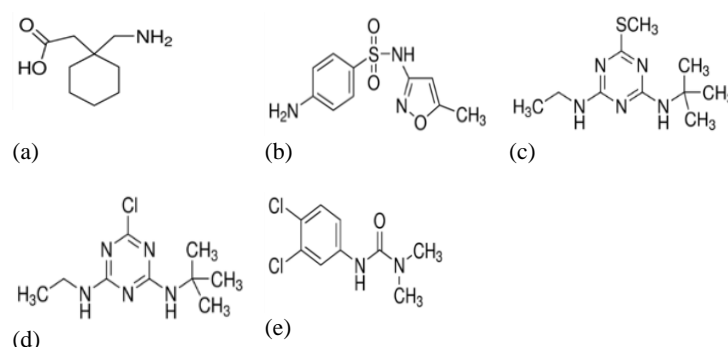


Figure 1. Chemical structure of (a) Gabapentin; (b) Sulfamethoxazole; (c) Terbutryn; (d) Terbutylazine; (e) Diuron.

Solid phase extraction (SPE) and liquid-liquid extraction (LLE) are widely used methods to extract organic analytes from aqueous matrices [11]. Extraction is followed by several complex techniques for the quantitative estimation using various instrument with relevant procedures, including gas chromatography (GC), mass spectrometry (MS), tandem mass spectrometry (MS/MS), liquid chromatography (LC), and high-performance liquid chromatography (HPLC), and these can be seen in Table 1. Though these methods produce high recovery, in contrast, it appears cost and time consuming if the study interest is only fixed to specific given compounds.

Table 1. Previous study of analyte's quantification

Analytes	Method	Recovery (%)	Citation
Gabapentin	GC/MS	<70	[12]
	SPE(GC/MS)	>99	[13]
	HPLC	100±3	[14]
	LC/MS	>99	[15]
Sulfamethoxazole	SPE(UV-HPLC)	89.2-97.3	[16]
	ILATPS + HPLC	92.0-99.8	[4]
	SPE(DLLME)+UHPLC/MS	95.3-96.4	[17]
	Online SPE-LC-MS/MS	>75	[18]
	HPLC	88.5	[19]
	LC/MS	>81	[20]
Terbutryn	Online superheated extraction, chromatography	103	[21]
	HPLC-DAD	>93	[22]
	Micellar Liquid Chromatography	>90	[8]
Terbuthylazine	HPLC-DAD	>86	[22]
	Micellar Liquid Chromatography	>85	[8]
Diuron	SPE-LC/MS	~100	[23]
	Micellar Liquid Chromatography	>90	[8]

SPE: SOLID Phase Extraction; HPLC-DAD: High-Performance Liquid Chromatography Diode Array Detector; ILATPS: Ionic Liquid Aqueous two-phase systems; DLLME- Dispersive Liquid-Liquid Microextraction.

Extraction and quantification of a given compound depend on its physicochemical properties. Gabapentin possesses high aqueous solubility (Table 3) therefore, a hypothesis is built for skipping the extraction of gabapentin using an organic solvent and determining its concentration directly from the aqueous solution. Sulfamethoxazole has 610mg/l water solubility (Table 3), therefore, this compound has possibilities of direct detection by measuring the product of factor ($= \frac{\text{slope (methanol solvent)}}{\text{slope (water solvent)}}$). For other micro-pollutants, the suggested methods (shown in Table 1) are

complex to perform in the daily routine for a quick estimation. Consequently, this study aims to work upon the hypothesis and produce a feasible novel method for direct quantification of Gabapentin without incorporating extraction; feasibility of Sulfamethoxazole quantification in aqueous media and to advance an analytical method to extract Terbutryn, Terbuthylazine and Diuron (maximum recovery); quantify with UV-Vis spectrophotometer.

2. EXPERIMENTAL

Reagents and materials Analytical grade gabapentin, sulfamethoxazole, terbutryn, terbuthylazine and diuron were purchased from Sigma-Aldrich (UK). Other chemicals and reagents were obtained from Fisher Scientific (UK). All chemicals and reagents were used without further purification. Distilled water was generated by ELGA PureLab Option-R 7/15 pure water system (Veolia Water, France). The cartridges for extraction were purchased from Phenomenex®.

Spectrophotometry Thermo Scientific™ GENESYS 10S UV-Vis spectrophotometer was used for analysis. It utilizes a high-intensity xenon lamp and dual-beam optical geometry to deliver unsurpassed data quality. Firing pulses of light only when the instrument is taking a measurement, the xenon lamp provides strong illumination from the UV to the near-IR region of the spectrum with wavelength accuracy ±1nm.

Preparation of solutions The stock solution was prepared in distilled water/methanol with specifically weighed analytes (micro-pollutants) in powder form. Gabapentin and later sulfamethoxazole analysis were made in an aqueous medium. The

solutions were prepared on the same day and analysed. For spectra analysis, 1-10 µg/ml working solution was prepared by consecutive dilution of stock solution. To prepare a calibration curve, working solutions with concentration ranges of 0-1 µg/ml and 0-6 µg/ml were used.

Spectra analysis The working solution was scanned between 190-1100nm spectrum in UV-visible spectrophotometer. The baseline of reagents was considered in every scan, the noise level was taken into account to determine the spectrum. Gabapentin maximum absorbance lies in the visible range thus, ninhydrin reagent was used to produce a coloured product for an appropriate analysis. Other analytes were scanned [without reagents] for absorbance peak (λ_{max}).

Different aliquots of gabapentin solution were transferred into the volumetric flask mixing with ninhydrin reagent (0.2% in methanol solvent) and 1ml of 0.005M NaOH. The solution was heated in a water bath for 15 min at 75°C. Then, the solution was cool to room temperature and made up to mark using distilled water to obtain desired gabapentin concentration.

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Calibration curve For each analyte, a calibration curve was generated at two variable concentration ranges, 0-1 µg/ml and 1-6 µg/ml, respectively. The required aliquot of 100 µg/ml stock solution was taken in a volumetric flask. The blank and working solution for gabapentin were prepared using ninhydrin reagent as discussed above. The experiment was validated using the protocol given by the International Council for Harmonisation (ICH)[24].

Solid phase extraction (SPE) Different cartridges were used during the process. The solutions were prepared with distilled water and run for extraction following protocol is shown in Table 2. The working solution in distilled water prepared from 10 µg/ml stock solutions and extracted into an organic solvent to determine the effectiveness of extraction method adopted.

Table 2 Type of cartridge used and extraction method for recovery of analytes

Steps	Sulfamethoxazole	Terbutryn	Terbutylazine	Diuron
<i>Cartridge Description</i>	1	2	2	2
<i>Pre-Treatment</i>	Adjust pH to 9.0±0.5	-	-	-
<i>Condition</i>	6 mL(s) of Methanol	20 mL(s) of Acetonitrile	20 mL(s) of Methanol	20 mL(s) of Acetonitrile
<i>Equilibrate</i>	6 mL(s) of 100mM Ammonium Acetate, pH 9.0	20 mL(s) of Distilled Water	20 mL(s) of Distilled Water	20 mL(s) of Distilled Water
<i>Load</i>	Sample	Sample	Sample	Sample
<i>Wash 1</i>	6 mL(s) of 100mM Ammonium Acetate, pH 9.0	20mL(s) of 20:80 Methanol: Distilled Water	20mL(s) of 20:80 Methanol: Distilled Water	20mL(s) of 20:80 Methanol: Distilled Water
<i>Wash 2</i>	6 mL(s) Methanol	-	-	-
<i>Dry</i>	5 min under full vacuum	10 min under full vacuum	10 min under full vacuum	10 min under full vacuum
<i>Elute</i>	6 mL(s) of 5:95 Formic Acid: Methanol	20 mL(s) of Acetonitrile	20 mL(s) of Methanol	20 mL(s) of Acetonitrile

¹: StrataTM-XL-A-100µm Polymeric Strong Anion, 500mg/6ml; ²: StrataTM-XL 100µm Polymeric Reversed Phase, 2g/20mL

3. RESULTS

Properties. Physio-chemical properties have an important role in determining the correct method to determine compound concentrations. Majorly, hydrophilicity is determined by Partition Coefficient (log P), lower the Log P value, higher the hydrophilic nature of the compound. And, basic and acidic dissociation

constants (pKa) are obtained from Phenomenex[®] method development tool site. These property parameters were considered when designing the appropriate methods and selecting the type of cartridges. Table 3 shows the properties of selected analytes.

Table 3 Physio-chemical properties of analytes

Micro-pollutant category	Name	CAS No.	Molecular formulae	Molecular weight (g/mol)	Basic pK _a	Acidic pK _a	Log P	Water solubility
<i>Pharmaceuticals</i>	Gabapentin	60142-96-3	C ₉ H ₁₇ NO ₂	171.24	9.91	4.63	-1.10	4.49×10 ³ mg/L at 25°C; <i>Soluble</i>
	Sulfamethoxazole	723-46-6	C ₁₀ H ₁₁ N ₃ O ₃ S	253.28	1.97	6.96	0.79	610 mg/L at 37°C; <i>Partly Soluble</i>
<i>Pesticides/ Biocides</i> <i>Continued Table 3</i>	Terbutryn	886-50-0	C ₁₀ H ₁₉ N ₅ S	241.36	5.72	14.31	2.88	25mg/L at 20°C; <i>Poorly soluble</i>
	Terbutylazine	5915-41-3	C ₉ H ₁₆ ClN ₅	229.71	3.18	14.17	2.48	5mg/L at 20°C; 9mg/L at 25°C pH 7.4; <i>Poorly soluble</i>
	Diuron	330-54-1	C ₆ H ₃ Cl ₂ NHCON(CH ₃) ₂	233.09	-	13.18	2.53	42mg/L at 25°C; <i>Poorly soluble</i>

CAS: Chemical Abstract Service; pK_a= -log₁₀ K_a (Dissociation constant); Log P: Partition coefficient

Gabapentin spectral characteristics. Gabapentin exhibits low absorption by conventional spectrophotometric methods[25]. UV-Vis spectrophotometer sensitivity reduces at the low wavelength, therefore; a coloured reagent should be employed. Ninhydrin reagent was taken as a substitute to attain precise and accurate Gabapentin estimation. Ninhydrin reagent readily reacts with the aromatic ring of Gabapentin via condensation reaction and develops a coloured product (Ruhemann's purple) [25]–[27]. But, the colour was not developed significantly over a varied concentration range. Hence, 1 ml of 0.005M sodium hydroxide was added. Sodium hydroxide aids gabapentin to react with ninhydrin via oxidative deamination of the primary amino group followed by the condensation of reduced ninhydrin to form coloured product[5].

Absorbance peak (λ_{\max}). Analytes wavelengths were scanned at 4200nm/min. Figure 2(a-f) illustrate analytes λ_{\max} of variable concentration range 1-10mg/l; Sulfamethoxazole solution prepared in methanol (Figure 2(b)), and distilled water (Figure 2(c)) showed nearly similar λ_{\max} 270nm, 265nm respectively. Thereby, the hypothesis to sulfamethoxazole estimation was approached for calibration of the solution in methanol and distilled water to witness the corresponding slope factor. Triazines have very similar λ_{\max} (Terbutryn: 225nm, Terbuthylazine: 224nm); it concludes both compounds if present in the mixture can mislead in determining the precise concentration. Gabapentin, Diuron showed absorbance peak at 281nm, 250nm respectively.

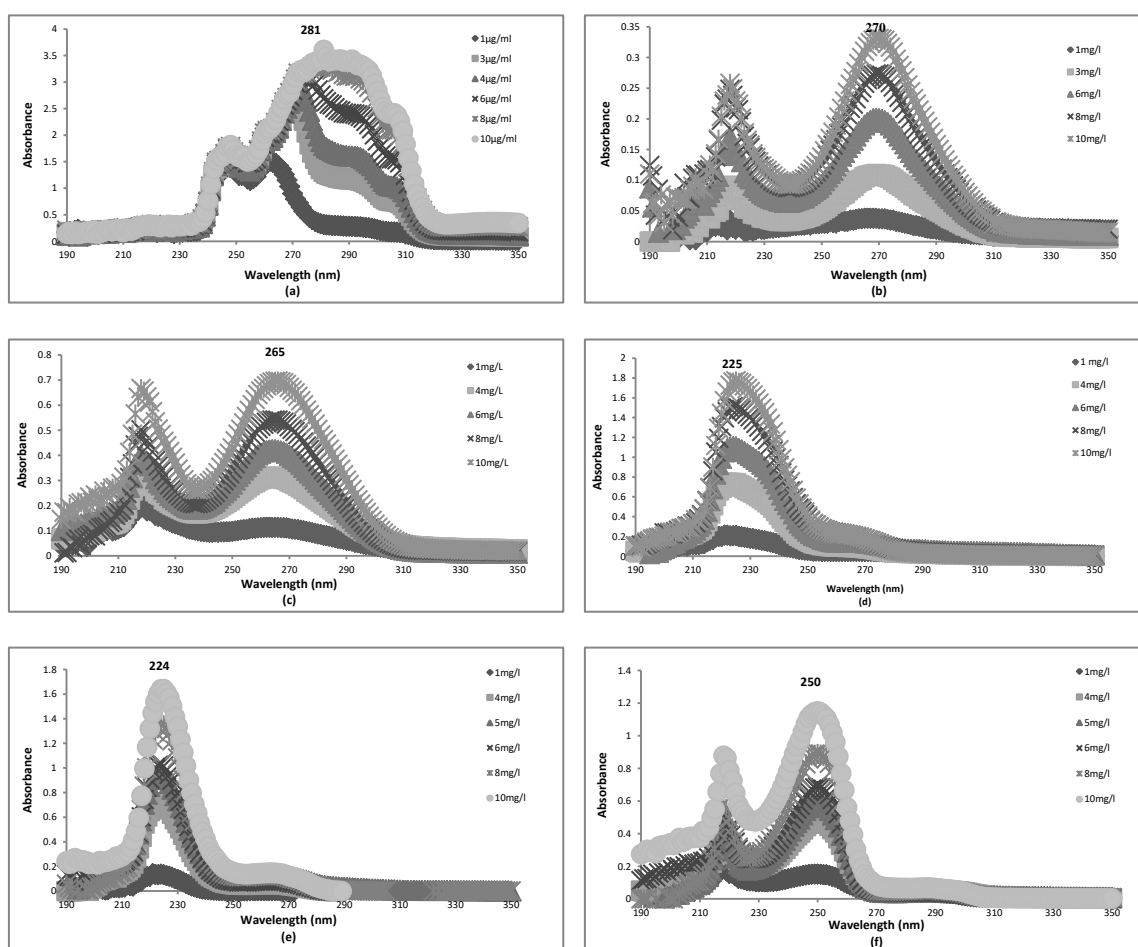


Figure 2. Absorbance peak (a) Gabapentin; (b-c) Sulfamethoxazole; (d) Terbutryn; (e) Terbuthylazine; (f) Diuron.

Calibration. To estimate the concentration of the analytes, the calibration curve between absorbance of the solution with the function of varied concentration from 0-1 and 0-6 $\mu\text{g/ml}$ was plotted in UV-Vis spectrophotometer. The representative calibration equation along with regression for each analyte is shown in Figure 3 (a-j). Calibration of sulfamethoxazole dissolved in methanol and distilled water is shown in Figure 3 (c). Slope

factor of both curves was 1.4 (acceptable); therefore, in laboratory scale when immediate concentration quantification of sulfamethoxazole in sample water is required, an alternative method can be employed by taking product of factor and concentration value from UV-Spectrophotometer. Moreover, in the study conventional extraction technique is also developed.

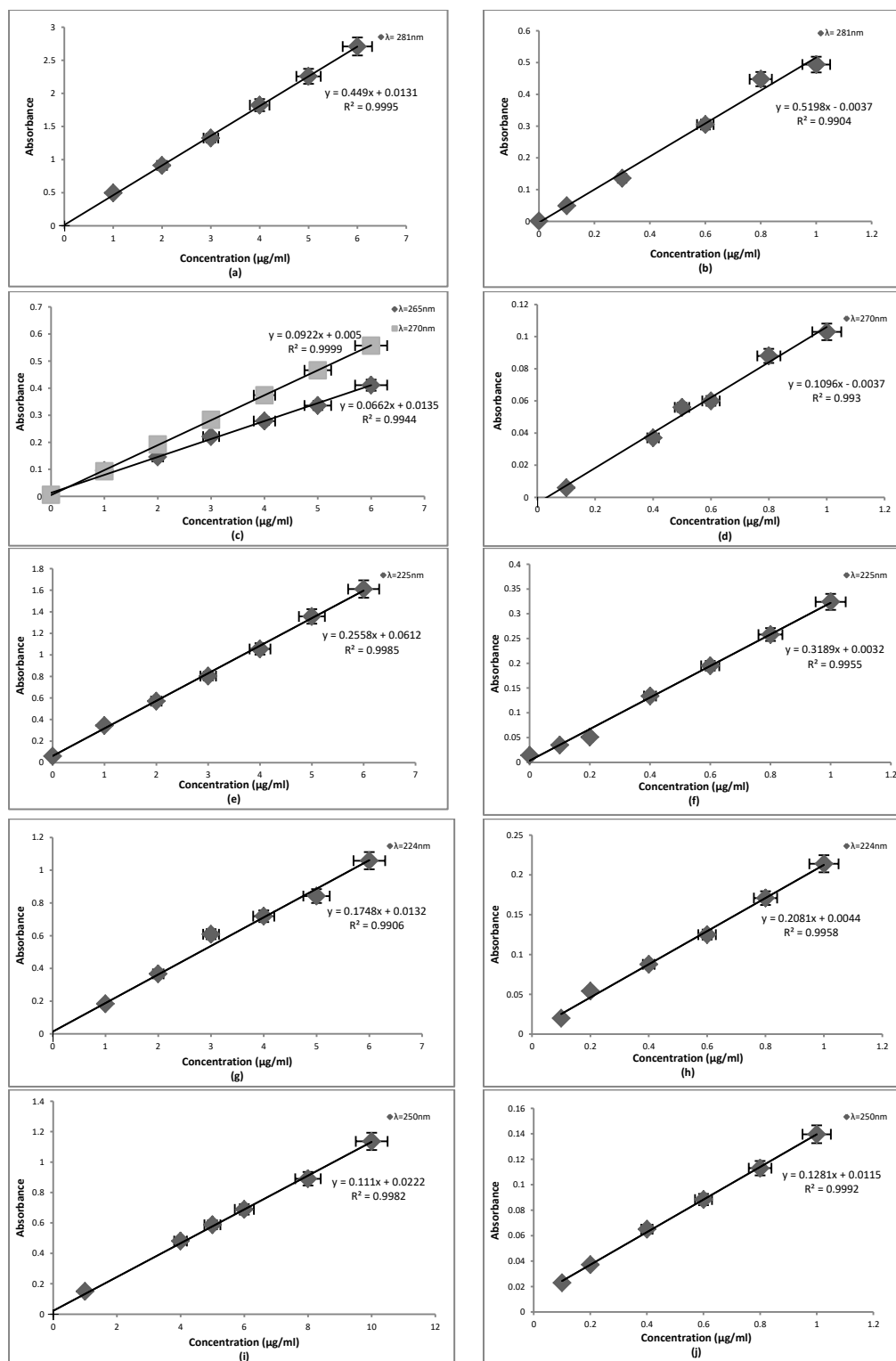


Figure 3. Calibration curve Gabapentin (a) 0-6µg/ml, (b) 0-1µg/ml; Sulfamethoxazole (c) 0-6µg/ml (at 270 and 265nm), (d) 0-1µg/ml; Terbutryn (e) 0-6µg/ml, (f) 0-1µg/ml; Terbutylazine (g) 0-6µg/ml, (h) 0.1-1µg/ml; Diuron (i) 0-10µg/ml, (j) 0.1-1µg/ml

Extraction and recovery of analytes. SPE was made as shown in Table 2. Elute obtained after extraction was analysed in UV-Vis Spectrophotometer against the calibration curve generated for respective analytes. Table 4 shows to present the maximum recovery achieved. Each extraction was run in triplicate to obtain reproducible results. The deviation between each observation is presented as % relative standard deviation (%RSD). We observed

that the recovery of compounds decreases with increase in concentration. Also, for low concentration small volume (compared to high concentration) is enough to obtain appreciable recovery. It can be related to water solubility/ hydrophilicity of micro-pollutants which contribute to the loss of recovery at higher concentration [28].

Table 4 Recovery of micro-pollutant after SPE

Micro-pollutant	Sample extracted		Recovery (%)	RSD (%)	RE* (%)
	$\mu\text{g/ml}$	mL			
Sulfamethoxazole	1	1000	83.6	11.7	0.2
	0.1	1000	96.0	9.7	0.0
	0.01	500	91.1	2.6	0.1
Terbutryn	1	1000	100.3	8.8	-0.3
Terbuthylazine	1	500	83.8	10.2	0.1
	0.1	500	88.5	7.3	0.1
Diuron	1	1000	106.3	7.7	-0.1

*RE: Relative Error

Statistical validation. Calibration curve was validated using regression statistics and determined Limit of Detection (LOD), Limit of Quantification (LOQ) in $\mu\text{g/ml}$ as shown in Table

5. Low value of sum of residuals square presents the accuracy of the regression equation developed for micro-pollutant calibration method using UV-Vis Spectrophotometer.

Table 5 Regression statistics of calibration method

	0-6($\mu\text{g/ml}$)				0-10 ($\mu\text{g/ml}$)
	Gabapentin	Sulfamethoxazole	Terbutryn	Terbuthylazine	Diuron
Multiple R	1.00E+00	1.00E+00	9.99E-01	9.95E-01	9.99E-01
R Square	1.00E+00	1.00E+00	9.99E-01	9.91E-01	9.98E-01
Adjusted R Square	1.00E+00	1.00E+00	9.99E-01	9.89E-01	9.97E-01
Standard Error	1.62E-02	1.63E-03	2.35E-02	4.03E-02	1.83E-02
Intercept	1.31E-02	5.03E-03	6.13E-02	1.32E-02	2.22E-02
Slope	4.49E-01	9.22E-02	0.26	0.17	0.11
LOQ	0.36	0.18	0.63	1.57	1.65
LOD	0.12	0.06	0.20	0.52	0.54
Sum of residuals square	2.84E-03	2.88E-05	2.76E-03	8.15E-03	1.68E-03
	0-1($\mu\text{g/ml}$)				
	Gabapentin	Sulfamethoxazole	Terbutryn	Terbuthylazine	Diuron
Multiple R	1.00E+00	9.97E-01	9.97E-01	9.98E-01	9.99E-01
R Square	9.90E-01	9.99E-01	9.95E-01	9.96E-01	9.99E-01
Adjusted R Square	9.88E-01	9.92E-01	9.95E-01	9.95E-01	9.99E-01
Standard Error	1.51E-02	2.41E-03	8.79E-03	5.27E-03	1.39E-03
Intercept	-3.74E-03	2.41E-03	3.19E-03	4.39E-03	1.15E-02
Slope	5.2E-01	1.10E-01	0.32	0.20	0.13
LOQ	0.29	0.22	0.16	0.19	0.22
LOD	0.10	0.07	0.06	0.06	0.07
Sum of residuals square	2.07E-03	6.48E-05	3.86E-04	1.11E-04	7.78E-06

4. CONCLUSIONS

The spectrophotometric method with preceding SPE has been successfully developed for the micro-pollutants found versatile in water. The method for quantification was checked for the accuracy and validated statistically. The average recovery (%) obtained are: Sulfamethoxazole 83.6($1\mu\text{g/ml}$), 96.0($0.1\mu\text{g/ml}$), 91.1($0.01\mu\text{g/ml}$); Terbutryn 100.3($1\mu\text{g/ml}$); Terbuthylazine 83.8 ($1\mu\text{g/ml}$), 88.5 ($0.1\mu\text{g/ml}$); Diuron 106.3 ($1\mu\text{g/ml}$). The proposed

method of direct quantification of gabapentin and sulfamethoxazole using UV-Vis Spectrophotometer is a novel approach and can be used instead of routine SPE. A knowledge advance with regards to the direct measurement of gabapentin in aqueous environmental condition is achieved through this study where no SPE procedures are required.

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